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AMENDMENT & RESPONSE		
Address to: Commissioner for Patents Washington, D.C. 20231	Application Number	09/628,472
	Attorney Docket Number	10003511-1
	Filing Date	July 31, 2000
	First Named Inventor	Wolber
	Examiner	B. Forman
	Group Art	1634
	Title	*Array Based Methods for Synthesizing Nucleic Acid Mixtures*

Sir:

This amendment is responsive to the Final Office Action dated April 24, 2001 for which a three-month period for response was given making this response due on or before July 24, 2002. In view of the amendments to the claims and the remarks put forth below, reconsideration and allowance are respectfully requested.

AMENDMENTS

IN THE CLAIMS

1. (Twice Amended) A method for producing a mixture of nucleic acids, said method comprising:

(a) providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on said array comprises a constant domain and a complement variable domain;

(b) hybridizing nucleic acids complementary to said constant domain with said array of single-stranded probe nucleic acids to produce a template array of overhang comprising duplex nucleic acids, wherein each overhang comprising duplex nucleic acid of said array comprises a double-stranded constant region and a single-stranded variable region overhang;

(c) subjecting said template array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence; and

(d) separating said mixture of nucleic acids from said template array.

5. (Twice Amended) A method for producing a mixture of a plurality of distinct deoxyribo-oligonucleotides of differing sequence, wherein each distinct deoxyribo-oligonucleotide of said plurality comprises a different variable domain V, said method comprising:

(a) providing an array of a plurality of surface immobilized distinct single-stranded probes, wherein each distinct surface immobilized single-stranded probe present on said array is described by the formula:

surface-L-R-F-cV-5'

C2

wherein:

L is an optional linking domain;

R is a recognition domain;

F is a functional domain; and

cV is a complement domain having a sequence that hybridizes under stringent conditions to a variable domain of one of said distinct oligonucleotides of said plurality;

(b) contacting said array of a plurality of surface immobilized distinct single-stranded probes under hybridization conditions with a population of nucleic acids of the formula:

5'-cR-cF-3'

wherein:

cR is the complement of R; and

cF is the complement of F;

whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex nucleic acid of said array is described by the formula:

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surface-L-R-F-cV-5'
                | |
          5'-cR-cF-3';
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(c) subjecting said template array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence; and

(d) separating said mixture of nucleic acids from said template array,

to produce said mixture of a plurality of distinct deoxyribo-oligonucleotides of

differing sequence, wherein each distinct constituent of said plurality comprises a different variable domain V.

REMARKS

Applicants respectfully request reconsideration of the application and allowance of Claims 1-15 (the only pending claims currently under examination) in view of the amendments and remarks made herein.

Amendments

Claims 1 and 5 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. At the Examiner's suggestion, the phrase "conditions under conditions sufficient" has been removed from the Claim 1. Claims 1 and 5 have been amended to clarify that the product of the primer extension reaction is a solution phase containing a mixture of nucleic acids, and that the product of the primer extension, i.e. the solution phase containing the mixture of nucleic acids, is actually separated from the template array.

Support for this amendment may be found throughout the specification, particularly in the Example on page 18. Step 3 of this example recites performing a T7 RNA transcription reaction, where an array is contacted with 250μl (i.e. a volume of 250 microliters) of a T7 transcription-providing solution and incubated overnight at 40°C. Steps 3 and 4 of the example recite removing the transcription solution after the overnight incubation, concentrating the solution, and loading the concentrated solution on a gel for analysis. The products are represented as a smear on the gel and therefore a mixture of nucleic acids is present in the reaction products. As such, the specification provides support for "a solution phase product of a primer extension reaction that produces a mixture of nucleic acids" and "separating the mixture of nucleic acids from the array". Accordingly, no new matter has been added to the specification.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

As such, entry of the above amendments is respectfully requested.

Rejection of claims 1-4 under 35 U.S.C. § 112, 2nd paragraph

Claims 1-4 were rejected under 35 U.S.C. § 112, 2nd ¶ as being indefinite for assertedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action asserts that Claim 1 is indefinite for the recitation "subjecting said template array ....to primer extension reaction conditions under conditions sufficient to produce said mixture of nucleic acids". Applicants respectfully traverse the rejection.

Claim 1 has been amended to recite "subjecting said template array ....to primer a extension reaction" in accordance with the Examiner's suggestion. As such, the step of "primer extension" is positively recited in the claim.

Applicants submit that the rejection of claims 1-4 under 35 U.S.C. § 112, 2nd ¶ has been adequately addressed in view of the amendment and remarks set forth above. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection of claims 1-4, 10-12 and 14 under 35 U.S.C. § 102(b)

Claims 1-4, 10-12 and 14 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Cantor, assertedly because Cantor discloses several methods for replicating an initial array of nucleic acids, one of which anticipates the claims. Applicants respectfully traverse the rejection.

Claim 1 has been amended to recite that the product of the primer extension reaction is a solution phase containing a mixture of nucleic acids, and that the product of the primer extension reaction, i.e., the solution phase containing the mixture of nucleic acids, is separated from the template array. As such, in order to anticipate claim 1, or any claim dependent therefrom, an anticipatory reference must disclose a primer extension reaction solution phase containing a mixture of nucleic acids, where the solution phase is separated from the template array.

In the cited Cantor section, Cantor is concerned with replicating an initial array of nucleic acids. Arrays of nucleic acids are structures in which a plurality of different nucleic acids are attached to a surface at different, known locations. In Cantor's replicating process,

while he does employ primer extension, a solution phase containing a mixture of product nucleic acids that are the products of a primer extension reaction is not taught. A solution phase containing a mixture nucleic acid products is extremely undesirable for Cantor since his method produces a replicated array, for which it is essential that, for each element of the array, nucleic acid products are kept separate. In other words, Cantor keeps each primer extension product separate from the others so that the replicated array can be produced. If this were not the case, and the reaction product of the array was a mixture separated from the template array, the product produced by the taught method would not be a replicated array. As such, Cantor does not teach a primer extension reaction solution phase containing a mixture of nucleic acids that is separated from the template array.

As such, because Cantor does not teach a product of a primer extension reaction that is solution phase containing a mixture of nucleic acids and separated from the template array, Cantor fails to teach all of the elements of Claim 1 and therefore fails to anticipate this claim. In addition, since Claims 2-4, 10-12 and 14 incorporate all of the limitations of Claim 1, Cantor fails to anticipate these claims as well.

Accordingly, Claims 1-4, 10-12 and 14 are not anticipated under 35 U.S.C. § 102(b) by Cantor and this rejection may be withdrawn.

Rejection of claims 5-9 and 13 under 35 U.S.C. § 103(a)

Claims 5-9 and 13 have been rejected under 35 U.S.C. § 103(a) as being obvious over Cantor in view of Dattagupta, assertedly because Cantor's method for producing a mixture of nucleic acids, in combination with Dattagupta's functional and recognition domain oligonucleotides, render the claims obvious to one skill in the art. Applicants respectfully traverse the rejection.

The M.P.E.P. teaches at §1242 that:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

As such, in order to establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by a reference or combination of references.

Furthermore, it is well established that a *prima facie* case of obviousness can be rebutted when the references actually teach away from the claimed invention. As the court explained[1]:

> [A] prima facie case of obviousness can be rebutted if the applicant (1) can establish the existence of unexpected properties in the range claimed, or (2) can show that the art in any material respect taught away from the claimed invention.

Thus, if the art teaches away from the claimed invention, the *prima facie* case of obviousness is rebutted.

The following analysis demonstrates that not only does the claimed invention possess elements not taught by the combination of Cantor in view of Dattagupta, but also that Cantor teaches away from the claimed invention. As such, the claimed invention is not obvious over the combined teaching of the references.

Claim 5 has been amended to recite that the product of the primer extension reaction is a solution phase containing a mixture of nucleic acids, and that the product of the primer extension reaction, i.e. the solution phase containing the mixture of nucleic acids, is separated from the template array.

As pointed out above, Cantor does not teach a product of a primer extension reaction that is solution phase containing a mixture of nucleic acids and separated from the template array.

Dattagupta appears to have been cited solely for the teaching of a functional and recognition domain. As such, Dattagupta fails to make up the above deficiency in the Cantor teaching.

In addition, because Cantor is concerned with replicating arrays, Cantor actually teaches away from producing a solution phase mixture of nucleic acids, where one must keep all of the different populations of primer extension products separate so that they can be placed on a substrate to produce the replicated array. As such, Cantor teaches away from the claimed invention

Because the combined teaching of Cantor and Dattagupta fails to teach a product of a primer extension reaction that is a solution phase containing a mixture of nucleic acids which is separated from the template array, and because Cantor actually teaches away from producing a solution phase mixture of nucleic acids, Claims 5-9 and 13 are not obvious over

[1] *In re Geisler*, 116 F.3d at 1469, 43 U.S.P.Q.2d at 1346

the combined teachings of these references and this rejection may be withdrawn.

Conclusion

The applicant respectfully submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Gordon Stewart at 650 485 2386. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

Date: 7.3.02

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